UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

HORIZON PHARMA IRELAND LIMITED, et al., Plaintiffs, v. ACTAVIS LABORATORIES, UT, INC., et al., Defendants.	Civil No. 14-7992 (NLH/AMD) **FED. R. CIV. P. 52(a)1 OPINION** **FILED UNDER SEAL**

APPEARANCES:

John E. Flaherty
Ravin R. Patel
Guillermo C. Artiles
McCARTER & ENGLISH LLP
Four Gateway Center
100 Mulberry St.
Newark, NJ 07102

Robert F. Green
Christopher T. Griffith
Caryn C. Borg-Breen
L. Scott Beall
Jessica M. Tyrus
Benjamin D. Witte
GREEN, GRIFFITH & BORG-BREEN LLP
NBC Tower, Suite 3100
455 North Cityfront Plaza Drive
Chicago, Illinois 60611

Dennis A. Bennett
GLOBAL PATENT GROUP, LLC
1005 North Warson Road, Suite 404
St. Louis, Missouri 63132
On behalf of Plaintiffs

Liza M. Walsh
Christine I. Gannon

Katelyn O'Reilly
WALSH PIZZI O'REILLY FALANGA LLP
One Riverfront Plaza
1037 Raymond Blvd., Suite 600
Newark, New Jersey 07102

Ralph J. Gabric
Mark H. Remus
Laura A. Lydigsen
Joshua E. Ney, Ph.D.
Joshua H. James
Andrew S. McElligott
BRINKS GILSON & LIONE
455 North Cityfront Plaza Drive, Suite 3600
Chicago, Illinois 60611
On behalf of Defendants

"It is not that every physical, chemical, or biological observable needs to have a complicated cause. But we would argue that in the complex dance of ingenuity that is modern science, in the gaining of reliable knowledge, one should beware of the inherent weaknesses of the beautiful human mind. The most prominent shortcoming is not weak logic, but prejudice, preferring simple solutions. Uncritical application of Ockham's Razor plays to that weakness. What is worse, it dresses up that weakness in the pretense of logical erudition."

Ockham's Razor and Chemistry[1]
Roald Hoffmann, Vladimir I. Minkin, Barry K. Carpenter

HILLMAN, District Judge

To be sure, Ockham's Razor[2] and the concept it encapsulates, is not directly relevant to the chemical formulation at issue in

[1] HYLE – An International Journal for the Philosophy of Chemistry, Vol. 3 (1997), 3-28. Copyright © 1997 by Elsevier, Paris.

[2] *Ockham's razor*, Merriam Webster's Collegiate Dictionary (11th Ed. 2006).

this Hatch-Waxman case. However, that concept – a preference for the known and for parsimonious explanations - and the observations of the philosopher-scientists who warn against oversimplification in assessing dynamic complex systems, does provide an interesting lens or paradigm by which one can address the relevant arguments of the parties in this case.

To the defendant and its expert, this is a simple case which largely involves the application of a few well-known and accepted general principles that when applied faithfully to a small set of defined variables readily explain how the improved patented chemical composition was predictably “optimized” from the patented earlier product. The plaintiff’s experts, on the other hand, describe a much more nuanced set of complex and interdependent circumstances in which the same defined variables and the principles applied to them predict little, both in theory and in practice, other than perhaps unpredictability itself.

The parties’ positions thus represent a spectrum and this line with opposites at each end is legally significant because a chemical composition that springs from mere routine experimentation on a known composition is likely obvious and therefore not a protectable invention. On the other hand, a product that overcomes unexpected results to combine in harmonious interplay previously known components in a unique and

beneficial way can be the inventive step the law protects.

This Court concludes, after hearing all the testimony and reviewing the exhibits accepted into evidence, that this case falls more toward the latter end of the spectrum. For that reason alone, defendant has failed to meet its high burden of overcoming the presumption of validity and establishing obviousness by the relevant legal standard.

A seven-day bench trial[3] was held involving Defendant Actavis Laboratories UT, Inc.'s infringement of claim 12 of Plaintiff Horizon's (Horizon Pharma Ireland Limited, HZNP

[3] The Court held oral argument on the parties' motions in limine on the morning of March 21, 2017. Trial was conducted in the afternoon of March 21, and then continued on March 22, 24, 27, 28, 29, and 30, 2017. Four witnesses testified at trial: Dr. Bozena Michniak-Kohn, Actavis's expert; Dr. Annette Bunge and Dr. Norman Weiner, Horizon's experts; and Dr. Edward Kisak, one of the patent's inventors. The parties also submitted fact testimony from Dr. Bradley Galer, Dr. John London, Dr. Jeffrey Sherman, Dr. Jagat Singh, Mr. Joseph Whalen, and Mr. Saleh Rifaat in the form of deposition designations. Post-trial submissions were filed by the parties on April 20, 2017. The 30-month stay of the FDA's approval of Actavis's ANDA expires on May 14, 2017. See In re Modafinil Antitrust Litigation, 837 F.3d 238, 243 (3d Cir. 2016) (citation omitted) ("If the brand manufacturer initiates a patent infringement suit, the FDA must withhold approval of the generic for at least 30 months while the parties litigate the validity or infringement of the patent; if the suit has concluded at the end of this 30-month period, then the FDA will follow the outcome of the litigation."); 21 U.S.C. § 355(j)(5)(B)(iii). The Court appreciates the professionalism and diligence shown by both sides in streamlining and expediting this proceeding without compromising the quality of their advocacy which was at all times helpful to this Court in understanding the law, concepts, and science at issue.

Limited and Horizon Pharma USA, Inc.) U.S. Patent No. 9,066,913 (the "'913 patent"). The '913 patent concerns PENNSAID® 2%, the first FDA-approved twice-daily topical diclofenac sodium formulation for the treatment of the pain of osteoarthritis ("OA") of the knees.[4] Actavis filed an Abbreviated New Drug Application No. 207238 ("ANDA") for its generic copy of PENNSAID® 2%, and contends that claim 12 of the '913 patent is not patentable because it is "obvious."[5] The Court issues this Opinion in accordance with Federal Rule of Civil Procedure 52(a)(1).[6]

DISCUSSION

A. Development of the '913 patent

Human skin is made up of several layers. Progressing from the outermost layer inward, these layers include: the *stratum corneum*, the viable epidermis, the dermis, and the hypodermis or

[4] This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331, 1338(a), 2201, 2202 and 35 U.S.C. § 271.

[5] Actavis stipulated to the infringement of claim 12 of the '913 patent if it is found valid. (Docket No. 313.)

[6] This Opinion constitutes the Court's Findings of Fact and Conclusions of Law pursuant to Rule 52(a)(1). Pierre v. Hess Oil Virgin Islands Corp., 624 F.2d 445, 450 (3d Cir. 1980) (holding that to be in compliance with Rule 52(a), findings of fact and conclusions of law do not need to be stated separately in a court's memorandum opinion); see also Ciolino v. Ameriquest Transp. Services, Inc., 751 F. Supp. 2d 776, 778 (D.N.J. 2010) (issuing an opinion which constituted the courts findings of fact and conclusions of law).

subcutaneous tissue. The skin also includes various structures that traverse several layers of the skin, including hair shafts, sebaceous glands, and sweat glands. The *stratum corneum* generally presents the greatest barrier to the passage of drugs through the skin. When drugs are applied topically, they permeate the *stratum corneum* by diffusing through the skin cells, by traveling down hair follicles and sweat glands, or both.

Topically applied drugs diffuse into and through the skin as a result of a concentration gradient. The concentration of the drug in the topical formulation is relatively high, compared to the concentration of the drug in the skin, and the concentration of drug decreases further in deeper layers of the skin. This concentration gradient creates a "driving force," which pushes the drug from the formulation into and through the skin.

At higher concentrations of the drug in the topical formulation, the rate of permeation through the skin also tends to be higher. Under Fick's First Law of Diffusion, a larger concentration of the drug in the topical formulation results in a larger concentration gradient, and leads to a greater permeation - or flux - rate of the drug through the skin.

When a topical formulation is applied to the skin, the amount of drug absorbed also depends on the volume of the

formulation that is applied. When a larger volume is applied, a greater amount of drug generally is absorbed. A thickened solution tends to increase the volume of the formulation on the skin because it will not run off the skin in the way that a liquid would.

Topical drug formulations commonly include some or all of the following components: an active ingredient, a solvent, a penetration enhancer, a humectant, and a thickening agent. Solvents are liquids that dissolve the active ingredient in a topical formulation so that the active ingredient can be absorbed into the skin. Penetration or permeation enhancers are compounds that enhance the absorption of the drug into and through the skin. Penetration enhancers act by various mechanisms, including by fluidizing the *stratum corneum*, increasing the solubility of the drug in the skin, by carrying the drug into the skin, and by evaporating or penetrating the skin, leading to an increase in the concentration of drug in the formulation remaining on the skin, which increases the concentration gradient driving the drug from the formulation and across the skin barrier. Humectants are non-volatile substances (i.e., substances that do not dry) which hold water onto the skin. Thickening, or gelling, agents generally are polymers that are added to topical formulations to increase the viscosity of the formulations.

The development of what would become PENNSAID® 2% was performed in multiple phases. The prior art, PENNSAID® 1.5%, approved by the FDA on November 4, 2009, was indicated for the treatment of symptomatic osteoarthritis of the knees, with the dosing regimen "40 drops four times a day." PENNSAID® 1.5% is an unthickened liquid solution that has a viscosity similar to water. This formulation has been in existence since 1986.[7]

The formulation of PENNSAID® 1.5% is as follows:

Ingredient	**PENNSAID® 1.5%**
Diclofenac sodium (active ingredient)	1.5%
Dimethyl sulfoxide ("DMSO") (penetration enhancer)	45.5%
Ethanol (solvent/penetration enhancer)	11.79%
Propylene glycol (solvent)	11.2%
Glycerin (humectant)	11.2%
Water (solvent)	To make 100%

[7] Prior to receiving FDA approval in the United States, PENNSAID® 1.5% was approved in Canada and several European countries for the treatment of symptomatic osteoarthritis of the knees, and by the early 1990s, more than 8,000 prescriptions had been written for PENNSAID® 1.5% for local treatment of arthritic pain in Canada alone. Before the FDA approved PENNSAID® 1.5%, the FDA had not approved of any other topical drug formulation containing dimethyl sulfoxide or "DMSO."

In 2005, the inventors of the '913 patent - Dr. Edward Kisak and Dr. Jagat Singh - were first asked by Nuvo Research Inc.[8] to make a thickened version of PENNSAID® 1.5%. In this first phase of the project, the inventors endeavored to identify a suitable thickener that could be added to the PENNSAID® 1.5% formulation to form a clear gel with a viscosity ideally between 500 to 2000 centipoise ("cp"). That range is similar to maple syrup (under 500 cp), motor oil (1000 cp), hand lotion (1500 cp), or honey (2000 cp). By way of comparison, PENNSAID® 1.5%, the unthickened liquid solution, had a viscosity of around 9 cp.

The inventors tried several thickeners, and found that the only thickeners that formed a clear and homogenous gel in PENNSAID® 1.5% were Carbopols. The inventors also found that the addition of a certain Carbopol increased the flux; that is, more of the active ingredient - diclofenac sodium – permeated the skin. According to Dr. Kisak, however, the Carbopol gels were also very touchy, at times did not swell properly, they clumped and had viscosities that would change over time.

[8] Nuvo Research Inc. developed PENNSAID® 2% and licensed U.S. sales and marketing rights to Mallinckrodt Inc., which applied for and, in January 2014, obtained FDA approval to make, sell, promote and market PENNSAID® 2% for use in the treatment of the pain of osteoarthritis of the knees. In October 2014, Horizon acquired the NDA for PENNSAID® 2%, and since January 2015, Horizon has been selling, promoting, distributing, and marketing PENNSAID® 2% in the United States.

Because of the increase in flux from the addition of Carbopol, Nuvo moved to a new goal for the project: developing a formulation that could be applied twice a day instead of the four times a day required by PENNSAID® 1.5%. Nuvo also made the decision to increase the concentration of the diclofenac sodium from 1.5% to 2%.

The inventors initially found that the increase in diclofenac sodium concentration from 1.5% to 2% had a destabilizing effect on the Carbopol gel formulations, but the second phase of development concluded with a formulation which contained 2% diclofenac sodium and 1.15% Carbopol 971. According to Dr. Kisak, there were still concerns that the Carbopol gel would not make a viable commercial product because of chemical impurity issues, long-term physical stability concerns, its tackiness, and its inability to dry well.

During phase three, the inventors varied the concentrations of the excipients propylene glycol, glycerin, ethanol, and water, and various thickeners were tested. The inventors varied propylene glycol from 0 to 11.2%, ethanol from 11.79 to 37%, glycerin from 0 to 11.2%, and water from 7.5 to 40%, and looked at a number of different thickening agents. During this phase, all of the different Carbopol gels failed due to various issues, such as a failure to gel entirely, separation, formulations which did not flow properly, physical stability, grittiness, as

well as the accelerated production of Impurity A, an impurity associated with diclofenac sodium.

Turning away from Carbopols, and after testing several cellulose gels that failed, the inventors were able to make stable gels with hydroxypropyl cellulose ("HPC") as the thickening agent. The inventors found, however, that if the ethanol concentration was reduced below approximately 25%, the gels would became hazy and prone to precipitation after prolonged storage.

During phase four, the inventors varied the ethanol concentration and cellulose thickener concentration to determine the impact on flux. The inventors determined that if they varied the ethanol concentrations from 21.1% to 29%, it did not affect statistically the flux. This formulation became the PENNSAID® 2% product claimed in claim 12 of '913 patent.[9]

[9] The '913 patent arises from U.S. Patent Application No. 14/497,096 ("the '096 application"), which was filed on September 25, 2014. The '913 patent is a continuation of U.S. Patent Application 14/025,781, filed on September 12, 2013, now the '809 patent, which is a continuation of U.S. Patent Application No. 13/564,688, filed August 1, 2012, now the '613 patent, which is a continuation of U.S. Patent Application 12/134,121, filed June 5, 2008, now the '838 patent, which is a continuation of International Application No. PCT/US2007/081674, filed October 17, 2007. The '913 patent also claims priority to U.S. Provisional Patent Application No. 60/829,756 ("'756 provisional application"), filed October 17, 2006.

Claim 12 of the ‘913 patent depends from claim 9, which depends from claim 8, which depends from claim 1, and claim 12 thus includes the following limitations:

> Claim 1: A topical formulation comprising:
> diclofenac sodium present at 2% w/w;
> DMSO present at about 40 to about 50% w/w;
> ethanol present at 23-29% w/w;
> propylene glycol present at 10-12% w/w;
> hydroxypropyl cellulose; and
> water to make 100% w/w,
> wherein the formulation has a viscosity of 500-5000 centipoise.
>
> Claim 8: The topical formulation of claim 1, wherein the DMSO is present at 45.5% w/w.
>
> Claim 9: The topical formulation of claim 8, wherein the hydroxypropyl cellulose is present at 2.5% w/w.
>
> Claim 12: A method for treating pain due to osteoarthritis of a knee of a patient in need thereof, said method comprising:
> administering to the knee a topical formulation of claim 9, wherein the administration of the formulation is twice daily.

The differences between PENNSAID® 1.5% and PENNSAID® 2% are:

Ingredient	**Prior Art PENNSAID® 1.5%**	**Formulation of ‘913 Patent, Claim 12**
Diclofenac sodium	1.5%	2%
Dimethyl sulfoxide (“DMSO”)	45.5%	45.5%
Ethanol	11.79%	23-29%
Propylene glycol	11.2%	10-12%
Hydroxypropyl cellulose (“HPC”)	-	2.5%
Glycerin	11.2%	Not required, but not excluded
Water	To make 100%	To make 100%

B. Analysis of Actavis's contention that claim 12 of the '913 patent is obvious

Horizon's '913 patent is presumed valid, including claim 12 independently. 35 U.S.C. § 282(a). Actavis contends that the patent never should have issued because the claimed invention was obvious at the time – October 17, 2006 - and, thus, one of the conditions of patentability was lacking.[10] See 35 U.S.C. § 103 (providing that a patent claim is invalid as obvious where the "differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains"). The burden of establishing invalidity of claim 12 in the '913 patent rests on Actavis. Id. Actavis must meet its burden by clear and convincing evidence. Microsoft Corp. v. I4I Ltd. Partnership, 564 U.S. 91, 97 (2011).

Four factors guide the obviousness inquiry under § 103: (1) "the scope and content of the prior art"; (2) "differences between the prior art and the claims at issue"; (3) "the level of ordinary skill in the pertinent art"; and (4) "[s]uch secondary considerations as commercial success, long felt but

[10] Based on the October 17, 2006 filing date of the '756 provisional application, the parties and their experts have assumed that the invention date for the '913 patent is October 17, 2006.

unsolved needs, [and] failure of others." KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 406 (2007) (quoting Graham v. John Deere Co., 383 U.S. 1, 17-18 (1966)).

"A prima facie case of obviousness typically exists when the ranges of a claimed composition overlap the ranges disclosed in the prior art," because the "overlap itself provides sufficient motivation to optimize the ranges." In re Applied Materials, Inc., 692 F.3d 1289, 1295 (Fed. Cir. 2012) (citations omitted). "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." Id. (citation omitted). A prima facie case of obviousness may be rebutted, however, "where the results of optimizing a variable, which was known to be result effective, are unexpectedly good." Id. (citing In re Boesch, 617 F.2d 272, 276 (Cust. & Pat. App. 1980)); see also In re Urbanski, 809 F.3d 1237, 1243 (Fed. Cir. 2016) (citing Applied Materials, 692 F.3d at 1297, 1298) (explaining that optimizing a variable is not obvious when it produces an unexpected result as compared to prior art, or when the variables interacted in an unpredictable or unexpected way).

Obviousness is a question of law based on underlying factual findings, including what a reference teaches, the existence of a reason to combine references, and whether the

prior art teaches away from the claimed invention. Urbanski, 809 F.3d at 1241.

Actavis argues that the changes made to PENNSAID® 1.5% which resulted in the PENNSAID® 2% formulation would have been obvious to a person having ordinary skill in the art ("POSA")[11] based upon the prior art available to the POSA as of October 17, 2006. More specifically, Actavis contends:

- PENNSAID® 1.5% was known to be safe and effective for treating osteoarthritis of the knee, but it was known to have several drawbacks, such as requiring frequent application and being vulnerable to run-off;
- a person of ordinary skill would have been motivated to modify the PENNSAID® 1.5% product to address these drawbacks by (1) increasing the amount of drug absorbed per application in order to reduce the application frequency and (2) thickening the PENNSAID® 1.5%

[11] Horizon's POSA would have had a bachelor's degree in pharmacy, chemistry, or a related discipline; an advanced degree in a related field; a few years of experience in the development of topical formulations; and access to a clinician experienced in treating patients with topical formulations; or a clinician with access to such a formulator. Actavis's POSA would have had an advanced degree, either a master's or a Ph.D., in pharmaceutics, pharmacology, or a related discipline, and would have had at least three years of experience in his or her field. The parties agree that using either POSA definition does not change their experts' opinions.

formulation and reducing its drying time in order to prevent run-off and improve the ease of application;

- a person of ordinary skill would have had a reasonable expectation that these modifications would address the known drawbacks of PENNSAID® 1.5%;
- PENNSAID® 1.5% included all of the ingredients required by claim 12 of the ‘913 patent except for a thickener;
- PENNSAID® 1.5% further included the claimed amounts of DMSO (45.5% w/w), propylene glycol (11.2% w/w), and water (to make 100% w/w); and
- the remaining limitations were disclosed in the prior art, such as Kasai, which disclosed ranges encompassing the claimed concentrations of diclofenac sodium (2% w/w), ethanol (23-29% w/w), and HPC (2.5% w/w), and Dow and Kamishita III, which disclosed the claimed viscosity (500-5000 centipoise).

Actavis argues that the three changes – and the two ingredients left unchanged – were obvious optimizations of result-effective variables that produced a predictable result, particularly as to the formulation’s absorption, thickness, and drying time. Actavis also argues that it would have been obvious to administer the claimed formulation in accordance with the method of claim 12, as Betlach discloses the claimed

application frequency of twice-a-day dosing, and a POSA would have reasonably expected that the claimed formulation would be effective for treating pain due to osteoarthritis of the knee when administered twice daily because each of the modifications leading from the PENNSAID® 1.5% formulation to the claimed formulation would have been reasonably expected to increase the absorption of diclofenac sodium at the site of action.

Unsurprisingly, Horizon argues that PENNSAID® 2% is not obvious because changes made to PENNSAID® 1.5% were not routine optimizations, and the results of the various changes could not be predicted based on prior art. Horizon contends:

- The effect of using multiple penetration enhancers is difficult to predict, as they can be additive or can compete with one another;
- numerous prior art publications demonstrate that the development of topical pharmaceutical formulations as of October 2006 was complex and unpredictable, because a complex system is one in which interactions between components including the drug and the vehicle can occur;
- a POSA as of October 2006 would have also known that PENNSAID® 1.5% consists of five different vehicle components (ethanol, glycerin, propylene glycol, water, DMSO), some of which can evaporate, all of which can

potentially interact with each other and with skin, and all of which could be absorbed into the skin, and thus the composition is constantly changing upon application as the components evaporate and absorb at different rates;

- a POSA would have understood that the differences between claim 12 of the ’913 patent and the prior art PENNSAID® 1.5% include: (1) the concentration of diclofenac sodium, (2) the concentration of ethanol, (3) the presence of glycerin, (4) the presence of a thickening agent, (5) the viscosity requirement, and (6) the method of administration, i.e., a reduction in dosing frequency to twice daily;
- but in order to arrive at the formulation recited in claim 12 of the ‘913 patent, a POSA would have had to (1) increase the diclofenac concentration from 1.5% to exactly 2%, (2) increase the concentration of ethanol from 11% to exactly the range of 23-29%, (3) add a thickening agent, (4) choose the thickening agent to be HPC, (5) identify the concentration of HPC to be exactly 2.5%, (6) select a viscosity range of between 500 and 5000 cps, and then (7) decide not to change the concentrations of DMSO or propylene glycol, but instead (8) remove or reduce glycerin and/or water to account for

the increases in diclofenac, ethanol and thickening agent concentrations and still total 100%, and the POSA would also have had to change the method of administration from 3-4 times per day to twice a day; and

- a POSA in October 2006 would have understood that when you increase viscosity of a topical formulation, it is harder for a drug molecule to move through the formulation and into the skin, and this can have a detrimental effect on flux.

The Court has thoroughly considered all of the evidence presented at trial and the parties' post-trial submissions. The Court accepts Actavis's position that prior art would have informed a POSA in October 17, 2006 of the various components to change in PENNSAID® 1.5% to improve upon that formulation's drawbacks, such as increasing the amount of drug absorbed per application in order to reduce the application frequency, making the formulation thicker to prevent run-off and improve absorption, and utilize penetration enhancers to reduce drying time and increase flux. The Court also accepts Actavis's position that a POSA would know from prior art, or even the POSA's general experience with formulating drugs, that: (1) glycerin hinders drying time, (2) ethanol reduces drying time, (3) ethanol can serve as a penetration enhancer, (4) HPC was an

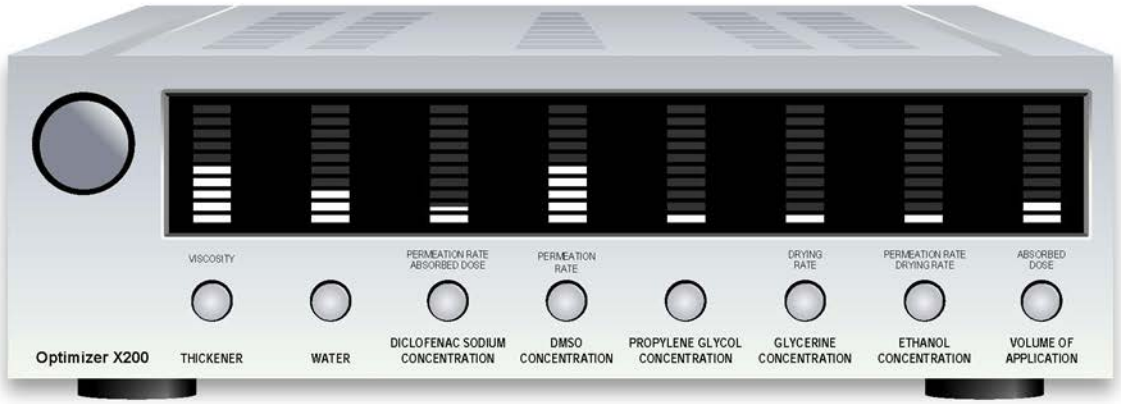
attractive thickener because it had been used in other diclofenac sodium formulations and formulations with other ingredients also found in PENNSAID® 1.5%, (5) an increase in concentration of diclofenac sodium can increase absorption, and (6) other diclofenac sodium formulations had been successfully applied less than four times a day resulting in the same daily therapeutic effect. The Court further accepts Actavis's position that prior art would have informed a POSA of compatible thickening agents and the suitable ranges for diclofenac sodium, ethanol, and HPC. All of these things flow logically from the prior art.

Even accepting all of the above, however, the Court finds that claim 12 in the '913 patent was not a result of routine optimization of PENNSAID® 1.5%. This is because general principles and ranges of permissible concentrations would not have predicted the exact formulation and dosing frequency that resulted in PENNSAID® 2%. A demonstrative used by Actavis's expert, Dr. Bozena Michniak-Kohn, illustrates the Court's conclusion.

Dr. Michniak-Kohn analogized the formulation of PENNSAID® 2% to a stereo receiver.[12] A typical, more vintage-style, stereo receiver has dials to adjust the bass, midrange, treble,

[12] "AV receiver," Wikipedia, https://en.wikipedia.org/wiki/AV_receiver (last visited May 12, 2017).

balance, and volume of the sound to suit a listener's preferences and achieve the best acoustics for a particular piece of music. Dr. Michniak-Kohn testified that drug formulation is like adjusting a stereo receiver, and the formulation of PENNSAID® 2% from the PENNSAID® 1.5% chassis was simply like turning the knobs to adjust the bass and treble to achieve the desired result, in this case the delivery of the active agreement to the desired spot under the skin and at the knee at a reduced dosing regimen. Dr. Michniak-Kohn created a graphic to visually explain her analogy:



(Docket No. 317-1 at 18.)

Dr. Michniak-Kohn explained that a POSA would have used her own knowledge about drug formulations and the available literature to perform a routine optimization of PENNSAID® 1.5% by turning up the dial for a little more diclofenac sodium, turning up the dial for ethanol by double, turning off the dial for glycerin, turning on the dial for HPC, leaving the dials for

DMSO and propylene glycol at their current setting, and turning the dial for water to sufficiently fill in the remainder. The credible evidence in this case demonstrates, however, that Dr. Michniak-Kohn's analogy fails for a least three reasons.

The first problem with defendant's analogy is the failure to differentiate between a system that allows independent change of one variable with little or no predicable or material effect on other variables and a system where the change to one variable must result in changes to the others. The latter is certainly more complex that the former. This not a case where a researcher could be assured that they had the ability to merely adjust, say the treble, without the need to adjust at least one or perhaps other variables as well. In the context of this case a drug formulator might be inspired by general knowledge and prior art to adjust one variable in the drug's composition but could do so only in a complex system in which the variables interact with each other in unpredictable ways.

More specifically, Dr. Michniak-Kohn's "Optimizer 300" fails to show that an adjustment to one PENNSAID® 1.5% ingredient does not automatically predict the impact, or need for adjustment, of the other ingredients. A formulation must total 100% w/w. Even a simple change of adding an additional 0.5% w/w of diclofenac sodium to the PENNSAID® 1.5% chassis would necessitate the reduction of another ingredient by 0.5%

w/w. What effect that change, or any other required change has on the desired effect is left unaddressed.

The goal of the invention here was to improve PENNSAID® 1.5% by making it a gel and reducing application frequency. To make a gel, the inventors needed to add a thickening agent. The addition of that ingredient, which was not in PENNSAID® 1.5%, required the reduction of another ingredient to maintain the 100% w/w. To increase flux so that more drug was absorbed by the skin, thereby allowing the product to only be applied twice a day, the inventors needed to increase the amount of a penetration enhancer. Again, another ingredient would need to be reduced to equal 100% w/w for the entire formulation.

The testimony of Plaintiff's expert, Dr. Annette Bunge, highlights this defect in Defendant's position in a way the Court finds convincing:

> Q. So now what's the difference between a simple solution and a complex one?
>
> A. . . . So, interactions can occur between the components of the formulation, so the drug and the vehicle can interact, that means they are changing the behavior of each other or at least the vehicle might be changing the behavior of the drug, the drug might change the behavior of the vehicle. It also means that the components of the formulation, the drug and the vehicle, are not interacting in any way with the skin.
>
> Now that we have these interactions, the state of the science is that we are not able to, in a quantitative or even really semi quantitative basis, represent what their effect would be, and so we are not able any longer to

predict dermal absorption, drug absorption or the drug flux.

Q. So, generally speaking, does adding more components to a topical formulation make it more complex?

A. Yes, it does. And so if we imagine a vehicle that contains five components, those components can all interact with each other or at least they may. Quite often one or more of them are volatile and will evaporate. Their evaporation rates are different. And in addition, all of the components have the possibility of absorbing into and through the skin. And so the concentration of each of the excipients in the vehicle is changing over time, because some of them are evaporating, some of them are absorbing, all of this is happening at a different rate. And that changes the interactions between all of these. So, this is an additional level of complexity that makes the system unpredictable in terms of the effect of making formulation changes to drug absorption, to predicting what drug absorption would be.

Q. And so then is it fair to say complex formulations don't have the same level of predictability that simple solutions do?

A. Yes.

(March 27, 2017 – Direct of Dr. Bunge, Page 742 line 11 to Page 743 line 20, Docket No. 336 at 131-132.)

Simply put, Dr. Bunge paints a much more accurate picture of the dynamic and complex formulation at issue in this case and the challenges in predicting the relative ratios of the various components a POSA would face in the effort to reach the desired goal. Dr. Michniak-Kohn’s analysis, while technically correct in the sense of the general and accepted concepts it begins with, fails to address, much less explain, the interrelatedness of the relevant variables.

The Defendant's stereo receiver analogy also fails in fully assessing the unpredictability that flows from applying the formulation, itself complex, in a similarly complex environment, in this case the vertically and horizontally multilayered organ of human skin, and adjacent areas of tissue and bone. Once again, the Defendant's "Optimizer 300" analogy begins with a truism but descends into a tangled web of more questions than answers.

For example, it is true that if one wants to increase the amount of bass frequencies one hears through the "Optimizer 300," increasing the level on the bass knob should have the desired effect. However, that signal boost must traverse the pre-amplifier into a power amplifier that transmits an analog electrical signal over strands of wire which, when attached to a paper diaphragm or cone, propagates a sound wave the rough equivalent of the original recorded sound. There is, in this process, many a slip between the cup and the lip.

The bass boost must not exceed the dynamic range of the power amplifier, the wires must be intact and not crimped, the connections secure, and the paper speaker must be efficient enough to physically move rapidly and accurately enough to reproduce the intended frequency. Any failure along the way

will distort or clip the final product.[13] Moreover, one setting for a piece of music in one room may not be the proper setting in a different room, depending on the room acoustics and other variables.

Once again, Dr. Bunge's ultimate opinion of non-obviousness more fully appreciates the lack of predictability of whether twice a day dosing could be achieved through the application of PENNSAID® 2% gel on and through a dense, at times impermeable, tangle of skin, tissue and bone:

> Q. Do you recall when Dr. Michniak-Kohn referred to this animation during her direct testimony?
>
> A. Yes, I do.
>
> Q. And what is it that this animation illustrates?
>
> A. So, she was illustrating the effect of the concentration driving force, so that the idea that the drug is present in the formulation at a high concentration, and that drives the drug into and through the skin and the body where the concentration is low. And she used this to illustrate the effect of a theoretical concept that helps us understand drug delivery into and through skin called Fick's law.
>
> * * *
>
> Q. So, in your opinion, what is Fick's law?
>
> A. So, Fick's law is sort of illustrated -- is described just in words at the bottom of this slide. I want to make one correction. The "area" term should not be there. It's already been incorporated into the flux. The flux is the

[13] "AV receiver", Wikipedia, https://en.wikipedia.org/wiki/AV_receiver (last visited May 12, 2017)(factors to be considered in rating amplifier output include distortion, headroom, speaker efficiency, among other things).

amount of drug per area that goes through the skin per time. So, it's just already incorporated. So, on the right-hand side of the equal sign, there should be two terms, the permeability coefficient and the concentration.

Now, Dr. Michniak-Kohn spent a lot of time talking about concentration. She didn't talk about the permeability coefficient very much except to say the units were centimeters per hour. But the permeability coefficient is the parameter that relates whatever the drug concentration is in the formulation to what the drug absorption would be.

Q. So, would a person of ordinary skill in the art need to consider the effect of formulation changes on this permeability coefficient?

A. Yes, they would, because formulation changes can change that permeability coefficient. In fact, they frequently do change it, except for very simple systems. In simple systems, then sometimes we know or at least it would be reasonably expected to be constant.

Q. So, if you increase drug concentration, will there be an effect on permeability coefficient?

A. In non-simple solutions, there can be, yes. And so that's -- and if we change formulations completely, so we go from a formulation, even a simple formulation A where we know it should be constant, to a different simple formulation where we know the permeability coefficient is also constant, the second simple solution will not usually have the same permeability coefficient as the first. So, two different simple solutions that have the same concentration almost always do not have the same drug absorption.

Q. And so in practice, if you're a person of ordinary skill in the art who is contemplating changes to a topical formulation, can you use Fick's law to help you predict what the changes to that formulation may be on drug absorption?

A. You can only use it if you have -- if you could predict the permeability coefficient you would have or how it might change with the formulation, and except for these very simple ones, simple solutions, that would not be possible.

> Q. Now, during his Honor's questioning of Dr. Michniak-Kohn last week, he asked a question about whether there existed simple guidelines. Are there simple guidelines that assist a person of ordinary skill in the art in predicting what the changes to a topical formulation would have on the permeability coefficient?
>
> A. So, for simple solutions, the guidelines would be that the permeability coefficient could be reasonably expected to be constant. If you had some data on what the drug absorption was for a given concentration, you could use that constant value that related the data you have to how the drug absorption would then change in further concentration changes.
>
> But if you have a complex formulation where the permeability coefficient will depend on all those interactions, so the interactions of excipient with the drug, the drug with the excipient, either one with the skin, they are changing the permeability coefficient, and so the guidelines there that are very simple ideas like some enhancers are known to affect certain elements of the skin, but those guidelines don't give us any information about what that value of that permeability coefficient would be, and without that kind of information, we can't predict what the relationship will be between drug concentration and drug absorption.
>
> Q. So, do the simple guidelines even give you any information about what the direction of change would be in the permeability coefficient in a complex topical pharmaceutical formulation?
>
> A. No, they do not.

(March 27, 2017 – Direct of Dr. Bunge, Page 749 line 16 to Page 750 line 1; Page 750 line 10 to Page 753 line 4, Docket No. 336 at 138-142.)

The import of this testimony is clear and is just one example of how Dr. Michniak-Kohn’s reliance on uncontroverted general principles oversimplifies the process that resulted in

the claimed invention. Both Dr. Michniak-Kohn and Dr. Bunge agree, as they must, that Fick's Law is just that, a time-tested, accepted, even venerated hornbook scientific principle that explains flux dynamics in simple solutions. But it is Dr. Bunge's testimony that establishes that it might not always work as predicted when a complex topical formulation attempts to drive an active ingredient across human skin, a surface Nature intended to be a formidable barrier against intruders.[14] Stated differently, Fick's Law is obvious. What that law predicts might actually happen in the actual factual scenario of this case is not.

---

[14] There are other examples in the record concerning the difficulties in achieving a therapeutic result for internal pain by use of a topical formulation:

> Q. All right. So, generally speaking, from topical formulations, about how much of the drug that's in the topical formulation actually crosses that skin barrier, the stratum corneum?
>
> A. Topical formulations are notoriously ineffective at delivering drug through the skin. It's quite common for only about 5 percent of the drug that's applied to the skin to actually go through the skin.
>
> Q. So, then what happens to the remainder of the drug from the topical formulation, the other 95 percent?
>
> A. It's left on top of the skin where it will either be washed off or fall off.

(March 27, 2017 – Direct of Dr. Bunge, Page 773 line 29 to Page 774 at 25, Docket No. 336 at 117-118.)

Finally, there is insufficient record evidence to support the Defendant's legal argument that the three changes to the PENNSAID® 1.5% formulation – and the two ingredients left unchanged – either in isolation or in combination were obvious optimizations of so-called result-effective variables that would produce a predictable result, particularly as to the formulation's absorption, thickness, and drying time. In the terms of Defendant's analogy, the tweaking of a formulation's "knobs" in this case did not result in the routine optimization of result-effective variables. Although individually adjusting one ingredient at a time may provide a predictable result, the combination of adjustments needed to change PENNSAID® 1.5% into PENNSAID® 2% was not predictable from the prior art.

One would search in vain for any reference in Dr. Michniak-Kohn's testimony to "result-effective variables." This is, of course, because this is a legal principle not a scientific one, but her opinions when juxtaposed with the Plaintiff's experts' testimony do not support that conclusion. Putting aside that there is ample record evidence that contradicts the result she predicts for individual variables from the prior art (for example, we have noted on another point regarding flux, that the prior art does not predict without contradiction that drug

concentration necessarily equates with increased permeation),[15] it is equally true that nowhere in the prior art, either singularly or in the cherry-picked manner of her discussion of the prior art for the noted variables, would a POSA find the schematic or roadmap to a diclofenac gel effective at two doses a day.

Dr. Bunge's testimony succinctly makes this point:

> Q. I want you to just follow with me from 50,000 feet, and then I'm going to ask you a question at the end that will allow to you elaborate a little bit on some of this.
>
> A. Okay. So, [drug] concentration could cause an increase [in flux], yes.
>
> Q. Right. And a person of ordinary skill in the art would know that ethanol was a known penetration enhancer, yes? Could be a penetration enhancer?

---

[15] Another example is the contention that increased ethanol enhances penetration. Again the record evidence establishes that the prior art would not predict this as a given:

> A. Yeah, so, what we've shown is that the prior art shows, for example, ethanol does not always increase absorption. It depends on what the other components are in the formulation.
>
> Q. All right. Okay.
>
> A. And ethanol, if we're adding it to dry faster, we have by design designed it so that the ethanol isn't there very long. So, the enhancement, by at least a lot of the mechanisms that are used to say it enhances, it has to be present, and so its effect would have to be very fast over a short time. And the difference in how effective it can be.

(March 28, 2017 – The Court's questioning of Dr. Bunge, Page 908 line 6 to line 16, Docket No. 337 at 48.)

A. Could be. There's certainly --

* * *

Q. Okay. And the person of ordinary skill in the art prior to the issuance of the patent would know that HPC had been used as a thickener in DMSO-containing formulations to form a gel?

A. Yes.

Q. And a person of ordinary skill in the art would know that glycerine was a humectant, and if your goal was to reduce drying time, the elimination of glycerine could enhance drying time?

A. Yes.

Q. Yes. So, taking all of those things together, that an increase in concentration could result in lower dosing, that ethanol could be a penetration enhancer, that HPC is likely to be an effective thickening agent, and the elimination of glycerine would increase drying time, why would a person of ordinary skill in the art not add two plus two plus two plus two plus two, whatever the numbers are, and come up with eight or 10, whatever it is?

A. Well, first of all, the prior art demonstrates unpredictability of formulation changes, even small ones, on the drug absorption, and in this case you have to have enough additional drug absorption sustained over twice as long in order to achieve the twice daily dosing. That's where -- so, already it's unpredictable. Many of these things might help, not all necessarily, but you have to have a reasonable expectation of succeeding to make it all the way to twice daily dosing. That's the high bar.

* * *

So, reaching enough additional drug absorption is difficult, and to get from four-times-a-day dosing to twice-a-day dosing with a reasonable expectation of success, a person of ordinary skill, understanding the unpredictability presented in the prior art about making such formulation changes in formulations of this complexity, would give them considerable pause about whether they could achieve that.

> They would have -- I don't -- my opinion is they would not have a reasonable expectation of success.

(March 28, 2017 – The Court's questioning of Dr. Bunge, Page 906 line 2 to line 9; Page 906 line 12 to Page 907 line 13; Page 908 line 17 to line 25, Docket No. 337 at 46-48.)

Even if the range of values for a particular variable was set out in the prior art and even if the combination of variables was itself predicted, the result will still not be obvious if the variables interacted in an unpredictable or unexpected way. KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 421 (2007); In re Applied Materials, 692 F.3d 1289, 1298 (Fed. Cir. 2012). Dr. Bunge's testimony convincingly establishes the unpredicted and unexpected results obtained from the changes made to the original PENNSAID® 1.5% formulation.

Although the parties debate the applicability of other authority in analyzing this point of law,[16] the Court's own research reveals a case more worthy of comparison. In Pfizer Inc. v. Mylan Pharmaceuticals Inc., 71 F. Supp. 3d 458, 468–69 (D. Del. 2014), aff'd 628 F. App'x 764 (Fed. Cir. 2016), former Chief Judge Sleet was confronted with a similar set of contrasting arguments. The science is not relevant here but Judge Sleet's mode of contrasting these two competing legal

[16] Auxilium Pharmaceuticals, Inc. v. Watson Laboratories, Inc., 2014 WL 9859224, at *1 (D.N.J. 2014).

principles is:

> Mylan argues that the asserted claims are obvious for two reasons: (1) a nearly identical analog of sunitinib was disclosed [in the prior art]; and (2) the lead compounds available as of the priority date would have motivated one skilled in the art to derive the claimed sunitinib malate. The court addresses each of these arguments in turn.
>
> Mylan argues . . . [the prior art] discloses approximately 1200 possible combinations . . . and instructs that each of the combinations will work, and therefore the "routine" steps of going from dimethyl sunitinib to sunitinib and finally to sunitinib malate were obvious . . . . Mylan relies on Merck & Co. v. Biocraft Laboratories, Inc. for this proposition. 874 F.2d 804 (Fed. Cir. 1989). In Merck, the Federal Circuit distinguished between compounds that are merely "obvious to try"—which are not barred by § 103—versus compounds with an expectation of success, i.e., compounds that will work for their intended purpose. Id. at 807. When a prior art reference lists a number of combinations, all of which should achieve the desired result, "routine" alterations or optimization will not preclude a finding of obviousness. Id. at 809.

Pfizer Inc., 71 F. Supp. 3d at 468.

After setting out the defendant's arguments, Judge Sleet rejects them finding, as this Court does here, that there was more that met the eye:

> The court finds, however, that Mylan's reliance on Merck goes too far. In Merck, the prior art reference disclosed individual diuretic agents that could be co-administered to achieve the desired properties. Id. at 807. The Federal Circuit found the patent-in-suit obvious in light of the prior art reference because the patentee **had merely followed the instructions and optimized the dosage levels.** Id. at 808–09. Similarly, in Mylan's other cited case, the claimed compound was simply a salt form of one of the compounds disclosed in the prior art, a step which was in fact suggested by the prior art reference. See Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348, 1367 (Fed. Cir. 2007) ("[T]he prior art provided not only the means of creating

> acid addition salts but also predicted the results, which Pfizer merely had to verify through routine testing.")
>
> The court is not convinced that the steps needed to go from dimethyl sunitinib ultimately to sunitinib malate constituted "routine optimization" on par with that in Merck or Pfizer. (D.I. 152 at 27–29.) Although Mylan states matter-of-factly that "the optimization of dimethyl to diethyl is even more routine and therefore obvious" than the steps taken in Merck and Pfizer, those cases **involved little more than following clearly delineated steps outlined by the prior art**. (Id. at 28.) Critical to the Federal Circuit's decision in Merck was the fact that "success [was] not dependent upon random variation of numerous parameters." Merck, 874 F.2d at 807. The court finds that the process of going from . . . . [the prior art ultimately to the claimed compound] . . . . **would have required significant guesswork and variation of parameters to achieve the end result**. **The [prior art] did not indicate that these steps would yield better [results], nor is the court convinced that the one skilled in the art would have found these "optimization" steps obvious without some data to support it. . . . [G]iven the sheer volume of possible combinations and the additional subsequent chemical alterations necessary to arrive at the claimed compound**, the court cannot say that one skilled in the art would have had a reason to [the prior art] as Mylan suggests. Thus, the asserted claims are not obvious in light of the [prior art].

Id. at 469 (emphasis added).

The analysis here is the same. Defendant's evidence does not show that the prior art showed "clearly delineated steps" that if taken and merely tweaked would achieve the desired result. Rather, as in Judge Sleet's Pfizer case, at best, a POSA would have been led to a wide range of possible penetration enhancers, humectants, thickening agents, and other components, each with strengths and weaknesses. Even then only broad ranges were disclosed and without any guidance on how to choose within

a range. All in the context of not knowing how choosing one component and at what concentration would compel a change to another component and, even if it stayed, what concentration would allow it to work harmoniously with the other variables. This is not routine optimization of a known formula proven in the prior art to achieve a particular result. As Dr. Kisak's testimony demonstrated, it was more akin to a crap shoot.

This Court must be vigilant in insuring that patent owners do not extend impermissibly the patent monopoly by the clever masking of routine and obvious improvements as something new and inventive. But it is equally true that the clarity of hindsight should not be used to deny an inventor the rewards of what the above-cited Dr. Hoffman, a Nobel laureate in Chemistry, has called the "complex dance of ingenuity." The weight of the record evidence – the phased history of the effort to improve PENNSAID® 1.5% to a gel of decreased dosage frequency – and the expert opinions proffered by the Plaintiff of the daunting hurdles overcome through experimentation satisfy this Court that the manner and method of getting there would not have been obvious to the relevant POSA and reflects a protectable step forward.

In sum, the Court must determine whether Actavis has shown through clear and convincing evidence that claim 12 of the '913 patent would have been obvious to a POSA as of October 17,

2006.[17] That changes are made to a complex formulation does not necessarily mean that such a formulation will never be deemed obvious simply because it is complex. But, "[f]ocusing on the obviousness of substitutions and differences, instead of on the invention as a whole, is a legally improper way to simplify the

[17] Because the weight of the evidence discussed above supports the finding that claim 12 of the '913 patent is not obvious, the Court does not need to consider the proceedings before the U.S. Patent and Trademark Office ("PTO"), other than to note that if the PTO had considered the prior art Actavis has presented here, Actavis would "ha[ve] the added burden of overcoming the deference that is due to a qualified government agency presumed to have properly done its job, which includes one or more examiners who are assumed to have some expertise in interpreting the references and to be familiar from their work with the level of skill in the art and whose duty it is to issue only valid patents." Shire LLC v. Amneal Pharmaceuticals, LLC, 802 F.3d 1301, 1307 (Fed. Cir. 2015) (citation omitted). Actavis would not have that extra burden, however, if the PTO was not provided with prior art relied up by Actavis. The Court also does not need to discuss whether Actavis's ANDA, which copies claim 12 of the '913 patent, is evidence of non-obviousness. Cf. Bayer Healthcare Pharmaceuticals, Inc. v. Watson Pharmaceuticals, Inc., 713 F.3d 1369, 1377 (Fed. Cir. 2013) (providing that "evidence of copying in the ANDA context is not probative of nonobviousness because a showing of bioequivalence is required for FDA approval"); Ortho-McNeil Pharmaceutical, Inc. v. Mylan Laboratories, Inc., 520 F.3d 1358, 1365 (Fed. Cir. 2008) (explaining that evidence of copying is a respected source of objective evidence of nonobviousness). Finally, the Court does not need to consider the secondary consideration of a "long-felt" but "unmet need." See AstraZeneca LP v. Breath Ltd., 88 F. Supp. 3d 326, 387 (D.N.J. 2015) (quoting Perfect Web Techs., Inc. v. InfoUSA, Inc., 587 F.3d 1324, 1332 (Fed. Cir. 2009) ("'Evidence that an invention satisfied a long-felt and unmet need that existed on the patent's filing date is a secondary consideration of nonobviousness.'")) (citing B.F. Goodrich Co. v. Aircraft Braking Sys. Corp., 72 F.3d 1577, 1583 (Fed. Cir. 1996) ("If prior art products were effective for the purpose of the claimed invention, there is no long-felt need.")).

often difficult determination of obviousness." Gillette Co. v. S.C. Johnson & Son, Inc., 919 F.2d 720, 724 (Fed. Cir. 1990). Even though a POSA in October 2006 would have recognized PENNSAID® 1.5%'s drawbacks and would have been aware of potential ways to alter PENNSAID® 1.5% to ameliorate those drawbacks, the changes to PENNSAID® 1.5% which resulted in the PENNSAID® 2% product were a result of optimizations that did not derive from routine experimentation.

CONCLUSION

"Recognition of a need does not render obvious the achievement that meets that need." Cardiac Pacemakers, Inc. v. St. Jude Medical, Inc., 381 F.3d 1371, 1377 (Fed. Cir. 2004). Such is the case here. For the reasons stated, Actavis has not shown by clear and convincing evidence that claim 12 of the '913 patent is invalid for obviousness under 35 U.S.C. § 103.

Horizon is directed to provide to the Court a proposed form of Order and Judgment. This Opinion shall remain under seal until the resolution of the parties' motions to seal their submissions relating to the trial. In their motions to seal, the parties shall indicate which, if any, portions of this Opinion should be redacted in accordance with Local Civil Rule 5.3.

Date: May 12, 2017
At Camden, New Jersey

s/ Noel L. Hillman
NOEL L. HILLMAN, U.S.D.J.